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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,298	04/17/2007	Jaime Gosalvez Berenguer	U 016409-0	4147

140 7590 09/26/2008

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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
09/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,298	GOSALVEZ BERENGUER ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: The filing date of the foreign priority document listed is incorrect.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-13, and 16-17 drawn to a method to evaluate the integrity of chromatin/DNA and animal sperm.

Group II, claim(s) 14-15, drawn to a kit comprising a DNA denaturing solution, a lysis solution, and instructions.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of Group I, a method comprising steps of "a) treating a sample containing the sperm, with a solution of DNA denaturing solution, b) a single treating the sample in the solution with a lysis solution to extract the nuclear proteins, and c) evaluating the integrity of the chromatin/DNA of the sperm as the lysis solution does not contain protein denaturing detergents and essentially does not destroy the tail of the sperm," does not provide contribution over the prior art (see Donnelly et al., "Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human

spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561, particularly, pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay").

During a telephone conversation with Janet Cord on 9/5/08 a provisional election was made with traverse to prosecute the invention of I, claims 1-13 and 16-17. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants argued that the inclusion of further components of the method of Invention I into the kit of Invention II would overcome the restriction requirement. This is not found persuasive because a kit comprising a DNA denaturing solution, a lysis solution (which does not contain a protein denaturing detergent), and instructions, could be used in various methods other than that of Invention I. The kit could be used for purification of any type of cell, for isolating RNA, DNA, or protein, as well as other methods which involve filtration, chromatography, solid-phase binding, etc. It is noted that applicant's amendments dated 9/5/08, particularly, amending the purpose of the instructions, does not provide limitations which are given patentable weight (see MPEP 2112.01, III: "where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, **>367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)< (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art

reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.)"

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP

§ 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 1-13, and 16-17 are currently under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-13, and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The preamble of claim 1 states, "…chromatin/DNA *and* animal sperm," and it appears from the steps of the method that it should read, "...chromatin/DNA [in or of] sperm," however, it is not clear whether this is the applicants' intention.

b. Claim 1 is confusing because it cannot be determined what is encompassed by “a single treating…” in step (b). The phrase is grammatically confusing and correction is required.

c. Claim 1 recites the limitation "the nuclear proteins" in step (b). There is insufficient antecedent basis for this limitation in the claim.

d. Claim 1 is confusing because it cannot be determined what is encompassed by "evaluating the integrity of the chromatin/DNA of the sperm *as the lysis solution does not contain protein denaturing detergents and essentially does not destroy the tail of the sperm*." The phrase seems to be joining two different steps/limitations of the method (noted as non-italicized and italicized above), which render the step confusing when combined. It appears that “*as the lysis solution does not contain protein denaturing detergents and essentially does not destroy the tail of the sperm”* should instead be in a wherein clause at the end of the method, and not included in step c, however, it cannot be determined whether this is the applicants’ intention. Clarification is required.

e. Claim 7 is confusing because “DNA denaturing solution is acid,” is not proper grammar and it appears it should read, "DNA denaturing solution is *an* acid." Appropriate correction is required.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3-5, 7, 10, 12-13, and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Donnelly et al., "Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561.

Regarding claim 1, Donnelly et al. teach a method to evaluate the integrity of chromatin/DNA and animal sperm comprising a) treating a sample containing the sperm, with a solution of DNA denaturing solution (see pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay" - 4 mmol/l lithium diiodosalicyclate), b) a single treating the sample in the solution with a lysis solution to extract the nuclear proteins (see pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay" - lysis with a solution of 2.5 mol/l NaCl, 100 mmol/l Na2EDTA, 10mmol/l Tris, pH 10 with 1% Triton X-100 for 1 hour followed by the addition of 10mmol/l DTT for 90 min. (total of 150 min. treatment time)), and c) evaluating the integrity of the chromatin/DNA of the sperm (pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay" where DNA fragments are analyzed via electrophoresis and ethidium bromide staining), as the lysis solution does not contain protein denaturing detergents and essentially does not destroy the tail of the sperm (the lysis solution does not contain protein denaturing detergents; EDTA is well known in the art to be a chelator).

Regarding claims 3-4, and 16, Donnelly teaches the method wherein the lysis solution comprises a non-ionic non protein denaturing detergent (i.e. Triton X-100).

Regarding claims 5, Donnelly teaches the method wherein the lysis solution comprises sodium chloride between 1 and 3M, dithiothreitol (DTT) between 0.001 and 2M (i.e. Donnelly adds DTT to the lysis solution after 1 hour, therefore, at 1 hour the lysis buffer comprises DTT as well), 2-amino-2 (hydroxymethyl)-l,3-propanediol (Tris) between 0.001M and 2 M and Triton X-100 between 0.1% and 3% (see pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay", third paragraph).

Regarding claim 7, Donnelly teaches the method wherein the denaturing solution is an acid (i.e. lithium diiodosalicyclate).

Regarding claim 10, Donnelly teaches the method where after steps a) and b) there is a sample stain step (see pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay" - ethidium bromide staining).

Regarding claims 12-13, and 17, Donnelly teaches the method wherein the sample containing sperm is included in an agarose microgel (see pg.1554, "Determination of DNA integrity using a modified alkaline single cell gel electrophoresis (Comet) assay" second paragraph).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly et al., "Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561 in view of Fernandez et al., "DNA breakage detetion-FISH (DBD-FISH) in human spermatozoa: technical variants evidence different structural features," Mutation Research, 2000, Vol.453, pp.77-82.

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein step a) precedes that of b), or proceeds steps b) and c).

Fernandez et al. describe a method for evaluating the integrity of sperm DNA, which comprises a denaturing step prior to a lysing step (see pg.78, "Materials and methods," second paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Donnelly et al. to perform step a) before that of b) because Fernandez et al. demonstrate that other sperm DNA integrity assays denature DNA prior to lysing and therefore, the skilled artisan would have had a reasonable expectation of success in changing the order of the steps in the method of Donnelly et al. as part of routine optimization of the assay. Furthermore, MPEP 2144.04 IV C states that the "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results" (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946)).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed order of steps therein.

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly et al., "Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561.

The teachings of Donnelly are discussed above. Although Donnelly teaches that the lysis solution comprises 2.5 mol/l NaCl, 10 mmol/l Tris, 1% Triton X-100, and 10 mmol/l DTT (i.e. DTT is added to the lysis solution after 1 hour, therefore, at 1 hour the

lysis buffer comprises DTT as well), the reference does not teach where the pH is about 7.5 (he teaches a pH of 10). However, an ordinary practitioner would have recognized that the pH could be adjusted to maximize the desired results. As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific pH was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art (see MPEP 2144.05).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and include the claimed pH therein.

13. Claim 8-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly et al., "Differences in nuclear DNA fragmentation and mitochondrial integrity of semen and prepared human spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561, in view of either one of Revel et al., "Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects sperm from DNA damage and apoptosis caused by benzo(a)pyrene," Reproductive Toxicology, 2001, Vol.15, pp.479-486 or Fernandez et al., "The Sperm Chromatin Dispersion Test: A Simple Method for the Determination of Sperm DNA Fragmentation," J. Androl, Jan/Feb 2003, Vol.24, No.1, pp.59-66.

The teachings of the primary reference are discussed above. Donnelly does not discuss the method wherein the DNA denaturing solution comprises an acid selected from hydrochloric, acetic, nitric acid or a mixture thereof [claim 8], or wherein the solution comprises hydrochloric acid [claim 9].

Revel discusses a method of evaluating sperm DNA comprising using 1M HCl for DNA denaturation (see pg.481, “Immunohistochemistry”).

Fernandez et al. discuss a similar method of examining the integrity of DNA in animal sperm where they also use HCl to denature DNA (see pg.60 “SCD Test" second column).

One of ordinary skill in the art would have been motivated to modify the method of Donnelly et al. to use HCl as the acid denaturant rather than the acid of lithium diiodosalicyclate because it was conventional in the art at the time of the invention to use HCl to denature DNA when examining sperm DNA in various methods, which is demonstrated by Revel and Fernandez. Since Donnelly demonstrates the benefits of using an acid to denature sperm DNA and Revel and Fernandez each demonstrate that it was conventional in the art at the time of the invention to use HCl as an acid DNA denaturant, it would have been obvious to one skilled in the art to substitute one acid DNA denaturant for the other to achieve the predictable result of denaturing sperm DNA using an acid.

14. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly et al., “Differences in nuclear DNA fragmentation and mitochondrial integrity of semen

and prepared human spermatozoa," Human Reproduction, 2000, Vol.15, No.7, pp.1552-1561 in view of Kruger et al., "New Method of Evaluating Sperm Morphology with Predictive Value for Human In Vitro Fertilization," Urology, 1987, Vol.30, No.3, pp.248-251.

The teachings of the primary reference are discussed above. This reference does not discuss the method where the staining is made with a Wright type solution.

Kruger et al. discusses a method for staining sperm in order to evaluate their concentration, motility, velocity, and morphology which uses a Wright Type solution (i.e. Diff-Quick, pg.249, first column, last paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Donnelly et al. to use a Wright Type Solution when staining rather than the ethidium bromide staining during electrophoresis because Kruger et al. demonstrate that using Wright Type Solutions (i.e. Diff-Quick) was conventional practice in the art at the time when staining sperm DNA. Since Donnelly demonstrates the benefits of using staining the sperm DNA and Kruger demonstrate that it was conventional in the art at the time of the invention to use Wright Type Solutions to stain sperm DNA, it would have been obvious to one skilled in the art to substitute one stain for the other to achieve the predictable result of evaluating the sample via staining.

Summary

15. No claims are free of the prior art.

16. The following are noted as references of interest:

a. Richthoff et al., "The impact of testicular and accessory sex gland function on sperm chromatin integrity as assessed by the sperm chromatin structure assay (SCSA)," Human Reproduction, 2002, Vol.17, No.12, pp.3162-3169.

b. Donnelly et al., "The effect of ascorbate and α-tocopherol supplementation in vitro of DNA integrity and hydrogen peroxide-induced DNA damage in human spermatozoa," Mutagenesis, 1999, Vol.14, No.5, pp.505-511.

c. Donnelly et al., "Assessment of DNA integrity and morphology of ejaculated spermatozoa from fertile and infertile men before and after cryopreservation," Human Reproduction, 2001, Vol.16, No.6, pp.1191-1199.

d. Irvine et al., "DNA Integrity of Human Spermatozoa: Relationships with Semen Quality," J. Andrology, 2000, Vol.21, No.1, pp.33-44.

e. Sakkas et al., "Nature of DNA Damage in Ejaculated Human Spermatozoa and the Possible Involvement of Apoptosis," Biol. of Reprod., 2002, Vol.66, pp.1061-1067.

f. Agarwal et al., "Sperm Chromatin Assessment," Textbook of Assisted Reproductive Techniques, 2nd Edition, Editors: Gardner et al., Taylor & Francis Group, plc, London, UK, 2004, Chapter 7, pp. 93-106.

g. Colls et al., "Sequential G-banding FISH on human sperm chromosomes," Chromosome Research, 1997, Vol.5, pp.457-461.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Molly E Baughman/
Examiner, Art Unit 1637